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November 21, 2005

MAIL STOP APPEAL BRIEF-PATENTS
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Re: U. S. Patent Application Serial No. 10/790,658 entitled "*R(-)-Desmethylselegiline* and Its Use to Treat Immune System Dysfunction" by Cheryl D. Blume, *et al.* (Our Ref: SOM700/4-4CIP2CON2DIVUS/13004)

Dear Sir:

Enclosed for filing in the above-referenced patent application are the following:

1. Appeal Brief in triplicate, including Appendix A (26 pages each);

2. Credit Card Payment Form ($500.00); and

4. Postcard.

If the referenced authorization is inadvertently omitted or deficient, or should an overpayment be included herein, the Commissioner is authorized to appropriately deduct or credit the requisite amount from Vinson & Elkins L.L.P. Deposit Account No. 22-0365/SOM700/4-4CIP2CON2DIVUS/13004).

Very truly yours,

Margaret Sampson

Margaret J. Sampson

MJS/cp
Enclosures

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:
Cheryl D. Blume *et al.*

Serial No.: 10/790,658

Filed: March 1, 2004

For: R(-)-DESMETHYLSELEGILINE AND ITS USE TO TREAT IMMUNE SYSTEM DYSFUNCTION

Group Art Unit: 1615

Examiner: L.S. Channavajjala

Atty. Dkt. No.: SOM700/4-4CIP2CON2DIVUS/13004

Confirmation No.: 9575

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APPEAL BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In support of the appeal from the second rejection dated May 17, 2005, Appellant now submits this Brief.

I. REAL PARTY IN INTEREST

The real party in interest of the patent application that is the subject of this appeal is the assignee, Somerset Pharmaceuticals, Inc.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellant that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 26 and 34-62 are pending in the instant application and are the subject of this appeal. In a preliminary amendment filed on March 1 2004, Claims 1-25 and 27-33 were cancelled without prejudice and Claims 34-62 were added. All claims stand rejected by the Examiner. All claims have been twice rejected by Examiner. A first office action rejecting all claims was mailed on October 21, 2004. A second office action rejecting all claims was mailed on May 17th, 2005, and this rejection is presently appealed.[1] A Notice of Appeal was filed on September 16, 2005 to appeal the final rejection of Claims 26 and 34-62. A copy of Claims 26 and 34-62 on appeal is attached hereto as Appendix A.

IV. STATUS OF AMENDMENTS

No amendments have been filed after the rejection dated May 17, 2005, and no amendments are submitted with this appeal brief.

[1] Appellant notes that the rejections set forth in the 5-17-05 Office Action only reject claims 26, 34, and 38-62, but the Official Action Summary states that all claims (26 and 34-62) are rejected. Appellant assumes that the Examiner intended to reject all claims as stated in the Summary.

V. SUMMARY OF INVENTION

The invention defined by the rejected claims relates to methods of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of gamma-interferon ("γ-interferon") production by administering the R(-)-enantiomer of desmethylselegiline, or a pharmaceutically acceptable salt thereof, wherein such administration leads to an increase in γ-interferon production in the mammal (*see, e.g.*, p.8, lines 21-25). R(-)-desmethylselegiline may also be administered in a substantially enantiomerically pure state (*see, e.g.*, p.7, lines 9-10). In certain embodiments, the mammal is a human (*see, e.g.*, p.7, lines 14-15).

In the present disclosure, R(-)-desmethylselegiline, or pharmaceutically acceptable salts thereof, can be administered as a single dose or in a multiple dose regimen (*see, e.g.*, p.9, line 22). The daily dose of R(-)-desmethylselegiline, or pharmaceutically acceptable salts thereof, may be at least about 0.015 mg, calculated on the basis of the free secondary amine, per kg of the mammal's body weight (*see, e.g.*, p.9, lines 12-16). In other embodiments, the daily dose is between about 0.5 mg/kg and about 1.0 mg/kg, or at least about 1.0 mg/kg (*see, e.g.*, p.9, lines 16-17). R(-)-desmethylselegiline and its pharmaceutically acceptable salts may be administered orally, non-orally, parentally, transdermally, buccally, sublingually, intravenously, subcutaneously, or intra-peritoneally (*see, e.g.*, p.11, lines 11-17).

The methods of the claimed invention can be used to treat conditions produced by immune system dysfunction such as cancer and AIDS (*see, e.g.*, p.8, lines 23-25; p.38, lines 11-14). The methods can also be used to treat conditions produced by immune system dysfunction caused by cancer chemotherapy, vaccination, and infectious disease

(*see, e.g.*, p.8, lines 23-25; p.41, lines 4-6). In another embodiment, the methods can be used to treat conditions produced by age-dependent immune system dysfunction (*see, e.g.*, p.8, lines 23-25).

VI. ISSUES

The issues for determination in this appeal are:

1. Whether Claims 26 and 34-62 are unpatentable under 35 U.S.C. § 112 for lack of enablement.

2. Whether Claims 26 and 34-62 are unpatentable under 35 U.S.C. §103(a) as obvious over Borbe (J. Neural. Transm. Suppl. 1990) in view of Barton et al (J. Neurooncol.) and Balsa et al (Biochem. Pharmacol. 1987).

VII. GROUPING OF CLAIMS

Claims 26 and 34-62 are grouped together.

VIII. ARGUMENT

A. The Rejection Based on 35 U.S.C. § 112, First Paragraph, for Lack of Enablement Should Be Overturned

Claims 26, 34, and 38-62 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner argues that the "claims are broad as they encompass a number of 'conditions' that are stimulated or caused by immune dysfunction or immune deficiency." 5-17-05 Office Action, p. 2. The

Examiner then proceeds to consider enablement of the claims in view of the Wands factors, and argues that the claims do not comply with the enablement requirement.

When evaluating enablement, the judicial standard specifies that a claimed invention is enabled if a person of skill in the art can make and use the invention without undue experimentation. MPEP § 2164.01 (discussing *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)). "In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." MPEP § 2164.04 (citing *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993)).

The Examiner has not met her burden of establishing a reasonable basis to question the enablement provided for the claimed subject matter. Appellant asserts that the pending claims are enabled because it is well within the skill of a person in the art to determine whether a condition produced by immune system dysfunction is associated with reduced levels of γ-interferon production, and whether administering the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ-interferon production. The underlying complexity of the immune system does not mean that the pending claims are not enabled, contrary to the Examiner's unsupported conclusion. Measuring the levels of γ-interferon production in a mammal is well within the skill of one in the art, and does not require undue experimentation.

1. Nature of the Invention Does Not Weigh Against Enablement

The Examiner argues the "nature of invention is extremely complex in that it encompasses anticipating multiple complex diseases or disorders," and that the "breadth of the claims exacerbates the complex nature of the claims." 5-17-05 Office Action, p. 3.

But whether or not the claims encompass multiple complex diseases or disorders is irrelevant to the question of enablement of the present claims, since one of skill in the art will clearly be able to understand and practice the scope of the pending claims without undue experimentation. Appellant believes that the Examiner is inappropriately focusing on the complex nature of immune system dysfunction to reject the claims, rather than on the actual scope of the claimed subject matter.

Whether a claim is enabled is determined by evaluating whether or not one of ordinary skill in the art would be able to make and use the claimed invention based on the disclosure. MPEP § 2164.01. Thus, the real questions with respect to enablement of the presently pending claims are: (1) whether one of skill in the art can identify conditions that fall within the genus of conditions produced by immune system dysfunction associated with reduced levels of γ-interferon production without undue experimentation; and (2) whether one of skill in the art can identify an increase in γ-interferon production in a mammal after administration of the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof without undue experimentation. The answer to both of these questions is yes.

Reduced levels of γ-interferon production, and the role such reduced levels play in immune system dysfunction, is clearly understood in the art. The reference attached as Exhibit A in Appellant's Response to the Office Action dated October 21, 2004, filed January 21, 2005 (received by the USPTO on January 25, 2005), Billiau, A., *Interferon-γ: Biology and Role in Pathogenesis*, ADV. IMMUNOL. 62:61-130 (1996), clarifies the correlation of γ-interferon (IFN-γ) to conditions related to immune deficiency such as cancer and AIDS, as well as autoimmune diseases. The cytokine γ-interferon plays a

central role in the immune system, and immune dysfunction related to γ-interferon has been recognized in both immune deficiency and autoimmune diseases:

> Medical interest in IFN-γ stems from awareness that a prominent target cell of IFN-γ, the macrophage, occupies a central position in the immune system. Adequate function of the IFN-γ/macrophage system is essential for natural as well as acquired resistance to infection and cancer. Malfunctioning of the system is recognized to be instrumental in inflammatory and autoimmune disease. *Id.* at 62.

Thus, although immune system function "is a complex interplay of several interleukins or chemokines," γ-interferon has a central position in the immune system and is involved in both immune deficiency and autoimmune diseases. 10-21-04 Office Action, p. 3.

The claimed subject matter is directed to the novel discovery that administration of R(-)-desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ-interferon production. As stated in the specification, the ability of R(-)-desmethylselegiline to restore γ-interferon production supports the conclusion that this enantiomer of desmethylselegiline is able to treat certain conditions in a mammal produced by immune system dysfunction *i.e.*, those that are associated with reduced levels of γ-interferon production (*see* Example 11, beginning on p.38). Given that the malfunctioning of the IFN-γ/macrophage system is recognized to be instrumental in inflammatory and autoimmune diseases, the ability of R(-)-desmethylselegiline to restore IFN-γ production will "bolster a patient's normal immunological defenses [and] be beneficial in the treatment of a wide variety of acute and chronic diseases including cancer, AIDS, and both bacterial and viral infections." (*see* p.38, lines 12-14).

The Examiner ignores the well-defined scope of the claimed subject matter and focuses instead on the complexity of the potential underlying causes of the conditions

produced by immune system dysfunction to reject the claims. But this argument is inappropriate for questioning the enablement of the pending claims, and ignores the fact that one of skill in the art will be able to routinely determine whether a mammal with a condition produced by immune system dysfunction has reduced levels of γ-interferon production, and whether administering the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ-interferon production.

2. State of the Art Does not Weigh Against Enablement

The Examiner argues that "a reduction in gamma-interferon does not necessarily result in immune system dysfunction," and therefore, "the described or claimed conditions may or may not be caused by gamma-interferon reduction leading to immune dysfuntion [sic]." 5-17-05 Office Action, pp. 3-4. Appellant asserts that this argument presented by the Examiner is irrelevant to the question of whether the pending claims are enabled.

The claims are specifically directed to methods of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of γ-interferon production. The scope of the claims is not directed to those conditions that have reduced γ-interferon production but no immune system dysfunction. In addition, the underlying mechanism causing the condition is not being claimed; instead the claims are simply directed to treating conditions produced by immune system dysfunction that are associated with reduced levels of γ-interferon production. Since the scope of the claims is clear to one of skill in the art, and would not require undue experimentation to practice, the pending claims are enabled.

3. The Specification Gives Sufficient Guidance to One of Skill in the Art to Practice the Claimed Subject Matter

The Examiner next argues that the claimed subject matter is not enabled because the "instant specification provides no guidance with respect to the procedure of administering instant composition to mammals for treating any or all of the disorders claimed." 5-17-05 Office Action, p. 4. But this is simply not true. The specification provides sufficient guidance to *one of skill in the art* for administering the instant composition to mammals for treating any or all of the disorders claimed (*see* specification, p.9, line 8 to p.10, line 20). For example, on p.9, lines 8-21, the specification states:

> The optimal daily dose of R(-)DMS, S(+)DMS, or of a combination, such as a racemic mixture, of R(-)DMS and S(+)DMS, useful for the purposes of the present invention is determined by methods known in the art, *e.g.*, based on the severity of the disease or condition being treated, the condition of the subject to whom treatment is being given, the desired degree of therapeutic response, and the concomitant therapies being administered to the patient or animal. Ordinarily, however, the attending physician or veterinarian will administer an initial dose of at least about 0.015 mg/kg, calculated on the basis of the free secondary amine, with progressively higher doses being employed depending upon the route of administration and the subsequent response to the therapy... These guidelines further require that the actual dose be carefully titrated by the attending physician or veterinarian depending on the age, weight, clinical condition, and observed response of the individual patient or animal.

A person skilled in the art could readily determine the effective amount of R(-)-desmethylselegiline required to achieve a therapeutic effect based upon animal pharmacology and early phase clinical trials in humans, both of which are standard activities and practices in the pharmaceutical industry, and are permissible under MPEP § 2164.01(c). Enablement is determined from the perspective of one of skill in the art, and procedures for determining the effective amount of a particular drug to administer to a mammal are routine in this art.

The Examiner also argues that the specification "fails to provide any guidance or rationale showing that the claimed method is effective to completely treating [sic] any or all disorders produced by immune dysfunction, associated with reduced levels of gamma-IFN or to extrapolate the data provided to al [sic] immune dysfunction conditions, that are known to-date or yet to be discovered." 5-17-05 Office Action, p. 4.

Appellant submits that this is an improper rejection. The claims are drawn to 'treating a condition," and the Examiner has improperly inserted the limitation that the claimed method must "completely treat any and all disorders..." The methods of the claims are not described as total cures to any disease or condition, but rather as methods of treating. This subject matter is analogous to that in *In re Sichert*, 566 F.2d 1154, 1160, 196 USOQ 209, 212 (CCPA 1977), in which the appeal court used the analogy of over-the-counter ointment drugs which have the purpose of stimulating blood circulation. Use of an ointment to stimulate circulation and alleviate pain is not the same as treatment directed at curing the disease (arthritis) that has caused the condition. Furthermore, Applicants are not required to demonstrate "full treatment" of a condition prior to filing an application. This issue has been addressed by the Federal Circuit:

> Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings. *Scott v. Finney* 32 USPQ2d 1115, 1120

Therefore, there is no requirement for patentability that the claimed methods be effective to treat any or all conditions produced by immune system dysfunction associated with reduced levels of γ-interferon production. As the MPEP acknowledges: "The presence of inoperative embodiments within the scope of a claim does not

necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." MPEP § 2164.08(b). A person of skill in the art will be able to determine whether embodiments of the claimed invention are inoperative or operative without undue experimentation, because one of skill in the art can clearly determine whether the administration of R(-)-desmethylselegiline results in increased γ-interferon production.

4. Predictability of the Art and the Amount of Experimentation Necessary Do Not Weigh Against Enablement

Finally, the Action states that "the practitioner would turn to trial and error experimentation in order to determine the 'conditions' caused by immune system dysfuntion [sic] (associated with gamma-IFN) in mammals that would respond to the claimed method of treatment (employing the claimed composition)." But as clearly set forth in the specification, immune system dysfunction conditions associated with reduced levels of γ-interferon production are already well known to those of skill in the art, and any such conditions that did not respond to the claimed method of treatment by demonstrating an increase in γ-interferon production in the mammal, which could easily be identified by one of skill in the art, would not fall within the scope of the claim.

The specification sets forth that certain conditions produced by immune system dysfunction are associated with reduced levels of γ-interferon production. For example, AIDS and age-related immune system function loss are two representative examples of conditions associated with reduced levels of γ-interferon production (*see* specification, p.8, lines 23-25). Experiments can be performed by a person of ordinary skill in the art to measure γ-interferon production in a mammal, and determine whether the level of

production is less than standard values for the mammal. Such experiments would allow the person of ordinary skill in the art to identify conditions associated with reduced levels of γ-interferon production without any undue experimentation. Similarly, a person of ordinary skill in the art could easily identify conditions that did not respond to the claimed method of treatment as demonstrated by the absence of an increase in γ-interferon production. Such experimentation would be routine and not undue.

5. The Examiner Failed to Meet the Burden for Establishing a Proper Rejection Under §112

The MPEP dictates that "[a] specification disclosure which contains a teaching of the manner and process of ... using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C § 112, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." MPEP § 2164.04.

The Examiner has failed to establish that the scope of the disclosure and the scope of the claims are incongruent. Appellant's application describes the manner and process of using Appellant's claimed invention in terms which correspond to the claimed subject matter. The specification provides experimental data that supports Appellant's claims and shows that the administration of the R(-)-enantiomer of desmethylselegiline restores γ-interferon production (*see, e.g.,* pp.38-41). The specification also provides dosage ranges for the administration of the R(-)-enantiomer of desmethylselegiline when practicing Appellant's claimed invention (*see, e.g.,* p.9, lines 8-21, and pp.41-42).

Finally, Appellant's application describes conditions which may be treated through the administration of the R(-)-enantiomer of desmethylselegiline (*see, e.g.*, p.8, lines 21-25).

The Examiner has not questioned the veracity of any of the Appellant's statements nor the validity of the experimental data contained in the application. The Examiner also has not offered any explanation of "why [she] doubts the truth or accuracy of any statement in [the] supporting disclosure," if she has any such doubts. MPEP § 2164.04. Instead, the Examiner has inappropriately focused on the underlying complexity of the immune system, rather than focusing on the claim language and the corresponding enabling disclosure.

Based on the foregoing arguments, Applicant respectfully asserts that the 35 U.S.C. § 112, first paragraph rejection is overcome. The Examiner has failed to show that Appellant's claims are not commensurate in scope with Appellant's disclosure, or would require any undue experimentation by one of skill in the art. In addition, the Examiner has not questioned the objective truth of any of Appellant's enabling support for the claims. Therefore, the Examiner has not satisfied the burden for making an enablement rejection under the first paragraph of 35 U.S.C. § 112. Appellant therefore respectfully requests that the Board overturn the rejection.

B. The 35 U.S.C. § 103(a) Obviousness Rejection is Overcome

The Examiner has rejected claims 26, 34, and 38-62 as obvious over Borbe in view of Barton et al and Balsa et al. The Examiner argues that (1) Borbe teaches the oral administration of DMS to rats, which is an MAO-B inhibitor; (2) Barton associates immune dysfunction with conditions such as AIDS, Kaposi's sarcoma etc.; and (3) Balsa teaches that the activity of MAO-B is predominant in lymphocytes (L) and granulocytes

(G). The Examiner combines these references to conclude that "[o]ne of an ordinary skill in the art would have expected DMS, a monoamine oxidase inhibitor, to be effective in treating AIDS, tumors, cancers and other immune deficient conditions by inhibiting the action of MAO-B of immune cells i.e., lymphocytes and granulocytes."

But as Appellant demonstrates below, the Examiner has failed to establish a *prima facie* case of obviousness. First, the three references offer no teaching, suggestion, or motivation to combine their teachings to produce the claimed invention. Second, even if the references are combined (without any teaching, suggestion, or motivation), the references do not teach or suggest *all* elements of the pending claims. This failure to teach all of the elements in turn means that one of skill in the art would have no reasonable expectation of success by combining the three references. Further, the references, even if combined, arguably teach away from the claimed invention. Indeed, the Examiner fails to explain in her combination of the above three references why one of skill in the art would expect that inhibiting MAO-B activity in lymphocytes and granulocytes will treat conditions produced by immune system dysfunction that is associated with reduced levels of γ-interferon production. Appellant certainly does not understand how the Examiner has come to such a conclusion based on the disclosures of the three combined references. Therefore, Appellant must conclude that the Examiner is using hindsight reconstruction to combine the three references together, which is impermissible.

1. Establishing a *Prima Facie* Case of Obviousness

When setting forth an obviousness rejection, the MPEP clearly indicates that it is the Examiner who "bears the initial burden of factually supporting any *prima facie*

conclusion of obviousness." MPEP § 2142. The MPEP sets forth that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be a suggestion or motivation to combine the reference teachings either in the references themselves or in the general knowledge of one of ordinary skill in the art; (2) there must be a reasonable expectation of success; and (3) the references when combined must teach or suggest all the claim limitations. MPEP §§ 2142 & 2143. The Examiner bears the initial burden of factually supporting each of the three elements to establish a *prima facie* case of obviousness. Appellant asserts that the Examiner has failed to establish any of the three criteria for such a *prima facie* case.

2. Motivation or Suggestion to Combine the References

The motivation or suggestion to combine prong of the *prima facie* case for obviousness requires that the Examiner establish a suggestion or motivation to combine the reference teachings either within the references themselves, or within the knowledge of a person of ordinary skill in the art. MPEP § 2143.01. The Examiner has failed to present any suggestion or motivation to combine the reference teachings within the references themselves, or within the knowledge of one of skill in the art.

For example, Borbe is directed to the administration of R(-)-desmethylselegiline, an MAO-B inhibitor, to rats. The disclosure of Barton is completely unrelated to Borbe, in that there is no mention of R(-)-desmethylselegiline or MAO-B inhibitors. Barton instead studied neurological complications in patients with Kaposi's sarcoma, and found that opportunistic infections correlated with the degree of immune system dysfunction in a patient. The third reference cited by the Examiner, Balsa, is also unrelated to Borbe. While Balsa discloses that lymphocytes and granulocytes have MAO-B activity, there is

no mention of R(-)-desmethylselegiline. Balsa also does not provide any teaching about the consequences of inhibiting the MAO-B activity of lymphocytes and granulocytes. Balsa is also unrelated to Barton. The mere knowledge that lymphocytes and granulocytes are part of the immune system hardly provides the motivation to combine these references. Therefore, as set forth above, the three references combined by the Examiner offer no teaching, suggestion, or motivation to combine their teachings to produce the claimed invention.

Since the Examiner has not shown that the references themselves contain a suggestion or motivation to combine their teachings, she must present a "convincing line of reasoning as to why the artisan would have found the claimed invention to be obvious in light of the teachings of the references." MPEP § 2142 (*citing Ex Parte* Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)). But the Examiner has not provided any such convincing line of reasoning.

The Examiner argues that since "Balsa shows the activity of MAO-B in lymphocytes and granulocytes, the cell types that play a key role in immune system function and Barton teaches that immune deficiency is related to conditions such as cancer, neurological dysfunction, infection and AIDS....it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use DMS of Borbe for reducing the MAO-B activity in lymphocytes and granulocytes, which in turn play an important role in the development of immune deficient disorders such as Kaposi's' sarcoma, AIDS or other opportunistic infections because Barton associates immune dysfunction with conditions such as AIDS, Kaposi's' sarcoma etc., and Balsa teaches that

the activity of MAO-B is predominant in G and L cells, which can be effectively inhibited by deprenyl."

The Federal Circuit has made it clear that a finding of a suggestion or motivation to combine must be 1) specific and 2) based on objective evidence. *See In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (reviewing numerous cases discussing obviousness rejections). The Examiner has not made any specific factual findings to support her statement that the combination she sets forth above would have been obvious to one of skill in the art. Likewise, the Examiner has not discussed any objective evidence that supports a finding of a suggestion or motivation to combine within the knowledge of one of skill in the art. Instead, the Examiner has engaged in hindsight reconstruction and impermissibly combined three references together without any clear explanation of the rationale or logic of the combination.

Since the Examiner has not provided a specific and objective factual discussion supporting her finding of a suggestion or motivation to combine the references in the knowledge of one of skill in the art, nor shown such a suggestion or motivation in the references themselves, the Examiner has failed to meet the first criterion for establishing a *prima facie* case of obviousness.

3. Teach or Suggest All Claim Limitations

The Examiner bears the initial burden as an element of a *prima facie* case of obviousness of factually establishing that the references, when combined, teach or suggest *all* of the claim limitations. MPEP § 2142. The references combined by the Examiner, however, fail to teach all of the claim limitations of the pending claims.

As the Examiner admits, the references do not explicitly discuss a reduction in the levels of γ-interferon production, which is an element of each of the pending claims, or that the administration of R(-)-desmethylselegiline leads to an increase in γ-interferon production. Instead, the Examiner argues that "absent showing the evidence to the contrary, it is the position of the examiner that the claimed composition implicitly restores the levels of gamma-IFN." But the Examiner presents no evidence that one of skill in the art would have understood this from the combined references.

Appellant assumes that the above rejection made by the Examiner is an inherency argument. *See* MPEP § 2112. The MPEP is clear that when an examiner relies on a theory of inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112, Part III (*citing Ex parte Levy*, 17 USPQ.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)). The Examiner has provided no such basis in fact or technical reasoning to support her rejection. Instead, she attempts to shift the burden to Appellant, which is impermissible, by making the conclusory statement that "absent showing the evidence to the contrary, it is the position of the examiner that the claimed composition implicitly restores the levels of gamma-IFN."

Since the Examiner has not met her burden of establishing a *prima facie* case of obviousness, Appellant is under no obligation to submit evidence that the combined references do not implicitly teach the restoration of γ-interferon production. Without any evidence to support her rejection, Appellant need not present evidence to refute this

conclusory statement made by the Examiner. Therefore, once again, the Examiner has failed to meet another criterion for establishing a *prima facie* case of obviousness.

4. Reasonable Likelihood of Success

As stated previously, the Examiner bears the initial burden of factually establishing a reasonable expectation of success when combining the teachings of the references as an element of a *prima facie* case of obviousness. MPEP § 2142. As Appellant has already established, there is no motivation or suggestion to combine the cited references, and even if combined, the references do not disclose every element of the pending claims. Therefore, there can be no expectation of success. Furthermore, even if one of skill in the art were to combine the cited references, he or she would not arrive at the claimed invention because the references, in fact, teach away from the claimed invention, and thus cannot render the claims obvious.

The Examiner states that "[o]ne of ordinary skill in the art would have expected DMS, a monoamine oxidase inhibitor, to be effective in treating AIDS, tumors, cancers and other immune deficient conditions by inhibiting the action of MAO-B of immune cells i.e. lymphocytes and granulocytes." The Examiner provided no other discussion of the likelihood of success for combining the cited references.

The Examiner's statement that one of skill "would have expected DMS... to be effective" cannot satisfy the Examiner's burden. The Examiner has offered no factual evidence in support of a reasonable expectation of success in combining the references. Without such support the Examiner's broad sweeping statement is insufficient to meet the factual burden established by MPEP §2142 for showing a reasonable expectation of success. Since the Examiner has not factually established a reasonable expectation of

success in utilizing R(-)-desmethylselegiline to treat a condition produced by immune system dysfunction, she has failed to establish a *prima facie* case of obviousness.

As stated above, even if a person of skill in the art were able to combine the cited references, the references arguably teach this person away from the claimed invention. For example, Balsa discloses that lymphocytes and granulocytes in pig blood have MAO-B activity. There is no indication that the cells studied in Balsa are mutant or otherwise abnormal. Therefore, one of skill in the art would conclude that lymphocytes and granulocytes, when properly functioning in the immune system, have MAO-B activity. Why then would one of skill in the art conclude that inhibiting the natural MAO-B activity of lymphocytes and granulocytes would have beneficial results for an organism? Certainly, one of skill in the art would reasonably expect that interfering with the normal activity of immune cells would be more likely to have a bad result than a good result. Since Balsa does not disclose what effect inhibiting the MAO-B activity of lymphocytes and granulocytes would have on the immune system, there would be no way for one of skill in the art to answer this question. Therefore, the Examiner's use of hindsight reconstruction to supplement the disclosures of these references is undeniable.

In light of the above arguments showing the Examiner's failure to show a suggestion or motivation to combine the references, that the combined references teach or suggest all of the claim limitations, and a reasonable expectation of success for such a combination, Appellant asserts that the Examiner has failed to establish a *prima facie* case of obviousness and respectfully requests that the Board overturn the Examiner's rejection under 35 U.S.C. § 103(a).

IX. CONCLUSION

Appellant respectfully submits that based on the foregoing observations and arguments, all pending claims listed in the Appendix A are enabled and patentable. It is therefore respectfully requested that the Board overturn the Examiner's rejections.

Respectfully submitted,

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APPENDIX A

Claims 1-25 (Canceled).

Claim 26. (Previously presented) A method of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of γ-interferon production, which comprises administering to the mammal the R(-) enantiomer of desmethylselegiline, or a pharmaceutically acceptable acid addition salt thereof, at a daily dose, administered in a single or multiple dosage regimen, of at least about 0.015 mg, calculated on the basis of the free secondary amine, per kg of the mammal's body weight, wherein the administration of the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ-interferon production in the mammal.

Claims 27-33 (Canceled).

Claim 34. (Previously presented) The method of claim 26, wherein said R(-) enantiomer of desmethylselegiline is in a substantially enantiomerically pure state.

Claim 35. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is caused by infectious disease.

Claim 36. (Previously presented) The method of claim 26, wherein the immune system dysfunction is age-dependent.

Claim 37. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is AIDS.

Claim 38. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is cancer.

Claim 39. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is in response to a vaccine.

Claim 40. (Previously presented) The method of claim 26, wherein the daily dose is between about 0.5 mg/kg and about 1.0 mg/kg.

Claim 41. (Previously presented) The method of claim 26, wherein the daily dose is at least about 1.0 mg/kg.

Claim 42. (Previously presented) The method of claim 26, wherein the mammal is a human.

Claim 43. (Previously presented) A method of treating a condition in a mammal produced by immune system dysfunction caused by cancer chemotherapy which is associated with reduced levels of γ-interferon production, which comprises administering to the mammal the R(-) enantiomer of desmethylselegiline, or a pharmaceutically acceptable acid addition salt thereof, at a daily dose, administered in a single or multiple dosage regimen, of at least about 0.015 mg, calculated on the basis of the free secondary amine, per kg of the mammal's body weight, wherein the administration of the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ-interferon production in the mammal.

Claim 44. (Previously presented) The method of claim 43, wherein the R(-) enantiomer of desmethylselegiline is in a substantially enantiomerically pure state.

Claim 45. (Previously presented) The method of claim 43, wherein the mammal is a human.

Claim 46. (Previously presented) A method of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of γ-interferon production, which comprises administering to the mammal the R(-) enantiomer of desmethylselegiline, or a pharmaceutically acceptable acid addition salt thereof, wherein the administration of the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ-interferon production in the mammal.

Claim 47. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline is in a substantially enantiomerically pure state.

Claim 48. (Previously presented) The method of claim 46, wherein the mammal is a human.

Claim 49. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered orally.

Claim 50. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered non-orally.

Claim 51. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered parenterally.

Claim 52. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered transdermally.

Claim 53. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered buccally or sublingually.

Claim 54. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered intravenously.

Claim 55. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered subcutaneously.

Claim 56. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered intra-peritoneally.

Claim 57. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline is administered at a daily dose of at least about 0.015 mg/kg of the mammal's body weight, calculated on the basis of the free secondary amine.

Claim 58. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is caused by infectious disease.

Claim 59. (Previously presented) The method of claim 46, wherein the immune system dysfunction is age-dependent.

Claim 60. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is AIDS.

Claim 61. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is cancer.

Claim 62. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is in response to a vaccine.